IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Pastan et al.
Application No. 10/031,158
Filed: January 11, 2002
Confirmation No. 8170
For: T-CELL RECEPTOR Y ALTERNATE READING FRAME PROTEIN, (TARP) AND USES THEREOF
Examiner: Stephen L. Rawlings, Ph.D.
Art Unit: 1641
Attorney Reference No. 4239-61854-01

CERTIFICATE OF MAILING

I hereby certify that this paper and the documents referred to as being attached or enclosed herewith are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 on the date shown below.

Agent for Applicant(s)

Date Mailed November 11, 2004

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P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

DECLARATION OF DR. IRA PASTAN AND DR. JAY A. BERZOFSKY UNDER 37 C.F.R § 1.132

1. We, Ira Pastan, M.D. and Jay A. Berzofsky, M.D., Ph.D., have performed additional experiments relating to the above-identified application. Ira Pastan, M.D., is an inventor of the above-referenced application. Jay A. Berzofsky, M.D., Ph.D. is the Chief of Molecular Immunogenetics at the National Cancer Institute of the National Institute of Health. A copy of Jay Berzofsky's curriculum vitae is attached to this declaration.

It our understanding that claims 1-6, 10, 15-20, 24-28, 34-35 and 45-47 were rejected in the Office action dated August 5, 2004, as allegedly not being enabled by the specification. Specifically it is asserted that one of skill in the art would not know that TARP polypeptides, and immunogenic fragments thereof, could be used to treat cancer based on the specification.

2. TARP, and immunogenic epitopes of TARP, are enabled by the specification of the above-referenced application. The amino acid sequence of TARP is provided as SEQ ID NO: 14 of the specification. This amino acid sequence is 58 amino acids in length. Functional domains are disclosed in Figure 14. Epitopes are clearly described in the specification. For example,

epitopes are defined in the specification. The specification also discloses that epitopes of use are 8-10 amino acids in length and have anchoring residues. Specific configurations of use are disclosed, such as wherein the TARP polypeptides is 9 or 10 amino acids in length and has a leucine or methionine in the second position and valine or leucine in the last positions (see page 28, lines 28-33). In addition, biological methods of testing whether an epitope is immunogenic is also provided (for example, see page 17, lines 1-10 and pages 30-32). The selection of binding motifs that bind HLA-A2 is disclosed on page 28, line 25 to page 29, line 29). In addition, computer based programs for predicting MHC binding motifs (immunogenic epitopes) were well known to those of skill in the art at the time the provisional application was filed.

3. Using this information, which is disclosed in the specification, we prepared immunogenic fragments of TARP. A computer program was used to determine the sequence of HLA-A2.1 binding epitopes of TARP. Four different nine amino acid long wild-type peptides were first identified using the program. These peptides were (1) amino acids 29-37 of TARP (SEQ ID NO: 14), (2) amino acids 2-9 of TARP (TARP-2-9) (3) amino acids 22-30 of TARP (TARP-22-30), and (4) amino acids 27-35 of TARP.

The specification of the above-referenced application discloses that peptides with a high affinity for MHC are generally preferable (see page 32, lines 13-16). Thus, the ability of these peptides to bind HLA-A2.1 molecules was then tested using a T2 binding assay. HLA-A2.1-binding peptides were synthesized on a Model Symphony peptide synthesizer (Perkin-Elmer, Boston, MA) using conventional f-MOC chemistry and cleaved from the resin by trifluoroacetic acid. The purity and molar concentration were analyzed by reverse-phase HPLC on a C18 column using a gradient of 0.1% trifluoroacetic acid in water and 0.1% trifluoroacetic acid in acetonitrile, and were further purified by preparative reverse phase HPLC using a similar gradient. Full-length peptides were purchased from Multiple Peptide Systems (San Diego, CA) at >95% purity and were single peaks by reverse-phase HPLC. Peptides were dissolved in double-distilled water (DDW) or 20% DMSO in DDW, and then different concentrations of peptides were added into the culture of TAP-deficient T2 cells. After overnight culture of the cells in medium supplemented with β-2 microglobulin, cells were stained with anti-HLA-A2. Each assay was performed in triplicate assay and data in this figure are representative of two

experiments. Two of these TARP peptides, TARP-29-37 and TARP-27-35, showed measurable binding capacity to HLA-A2.1 molecules. These immunogenic peptides have the characteristics sequence disclosed on page 28, lines 27-33, namely they are nine amino acids in length and have a leucine in the second position and a leucine in the last position.

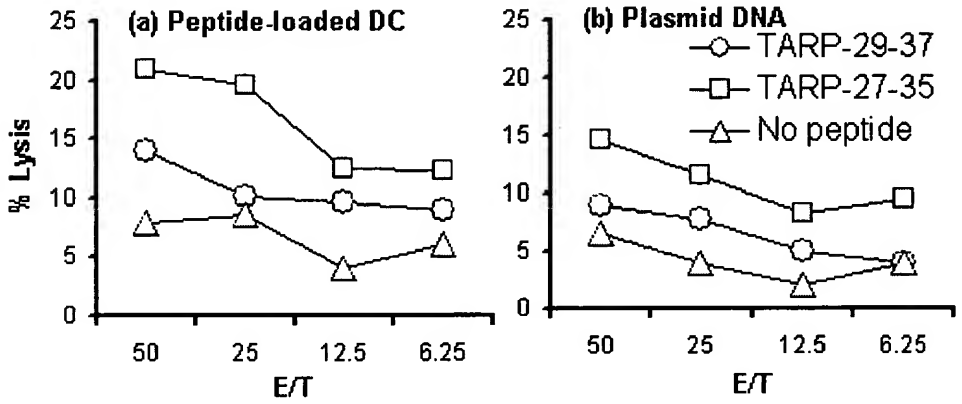
To demonstrate that these two TARP peptides were immunogenic, $A2K^b$ transgenic mice were then immunized with either peptide-pulsed dendritic cells (DC) or plasmid DNA expressing the TARP. The immunization of transgenic mice is disclosed in the specification on page 32, lines 5-8.

$A2K^b$ transgenic mice express a chimeric HLA-A2.1 transgene with the $\alpha 1$ and $\alpha 2$ domains from HLA-A2.1 and the $\alpha 3$ domain from $H2K^b$, to allow binding to mouse CD8, on a C57BL/6 background (Sherman et al., *Science* 258:815, 1992). Mice were immunized subcutaneously with peptide-loaded (10 μM of TARP-29-37 or TARP-27-35) bone marrow-derived DC and boosted twice at three-week intervals (see Fig. 1A). In addition, mice were immunized with 100 μg of DNA plasmid encoding these peptides intramuscularly and boosted four times at three-week intervals. Three weeks after the final immunization, spleen $CD8^+$ T cells were restimulated with splenocytes in media containing 10 μM soluble peptides for 7 days. In a 5h ^{51}Cr-release assay, Jurkat cells transfected with HLA-A2 were labeled with ^{51}Cr, and then pulsed with 10 μM of peptides. Without washing, target cells were mixed with different numbers of effector cells for 5h before harvesting. The results are shown in Fig. 1B. The result presented in Fig. 1A and 1B show that both TARP-29-37 and TARP-27-35 induced peptide-specific $CD8^+$ T cell responses in the mice immunized by either immunization protocol, although responses were higher after peptide-pulsed DC immunization.

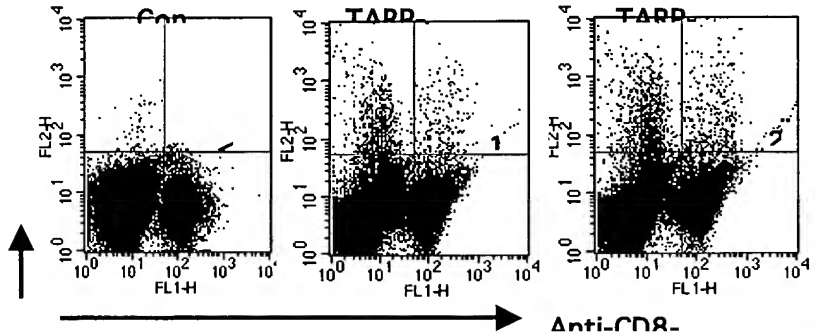
The expression of intracellular IFN-γ was also assessed. For intracellular cytokine staining, $CD8^+$ T cells from the mice immunized with peptide-pulsed DC were stimulated with the identical peptide and treated with Brefeldin A for 5 hours, and then cells were stained with anti-CD8-FITC and IFN-γ-PE as described in the manufacture's protocol (Pharmingen). In each experiment, pooled-spleen $CD8^+$ T cells of three mice were tested. The data shown in Fig. 1C are representative of two repeated experiments. Mice immunized with TARP-29-37 pulsed-DC

or TARP-27-35 also had a significant number of $CD8^+$ T cells producing IFN-γ. Thus, fragments of TARP are clearly immunogenic.

Figure 1: Immunization with peptide-loaded DC or a DNA plasmid expressing TARP results in peptide-specific $CD8^+$ T cell responses in $A2K^b$ transgenic mice



(c) Intracellular IFN-gamma staining



4. The reactivity of human T cells from a prostate cancer patient to TARP-29-37 and TARP-27-35 was then assessed. Assays to detect T cell responses are described in the specification of the above-referenced application on page 32, line 25 to page 33, line 2. To test for the presence of peptide-specific $CD8^+$ T cells in an HLA-A2.1-positive prostate cancer

patient, $CD8^+$ T cells from the leukapheresis of the patient donor were restimulated with peptide-pulsed autologous DC in several cycles. After at least six cycles of *in vitro* restimulation with both wild-type peptides (TARP-29-37 and TARP-27-35), $CD8^+$ CTL were detected. Cytolytic activity of those $CD8^+$ CTL raised with individual peptides was tested against peptide-pulsed C1R-A2.1 target cells. The $CD8^+$ CTL could lyse peptide-pulsed target cells specifically. These results demonstrate that TARP-29-37 and TARP-27-35 can be used to activate T cells from a subject with prostate cancer, and that these activated CTLs can lyse target cells.

5. Additional assays to test immunogenicity of peptides are disclosed in the specification at page 32-33. Such assays were used to evaluate the response of human CTL to TARP-29-37 and TARP-27-35.

Human $CD8^+$ CTL were raised against TARP-29-37 and TARP-27-35. The cytolytic activity of individual $CD8^+$ CTL was measured against target cells. These experiments demonstrated that human $CD8^+$ CTL raised with TARP-29-37 could recognize and lyse target cells pulsed with the wild-type epitopes.

To test whether those CTL could kill human tumor cells that endogenously express TARP, a CTL assay was performed against tumor cell lines that express both HLA-A2.1 and TARP. At a 50:1 E/T ratio, all $CD8^+$ T cells could kill the breast cancer line, MCF-7, but showed marginal (10-12 %) lytic activity against the prostate cancer cell line, LNCaP. Before CTL assay, all target cells were cultured in medium containing IFN-γ, and the expression levels of HLA-A2.1 before and after IFN-γ-treatment were measured. As expected from the CTL assay, LNCaP cells express an extremely low level of HLA-A2.1 and the level of HLA-A2.1 was not much increased by the culture of the cells in medium containing IFN-γ. It is likely that the low expression of HLA-A2.1 on LNCaP cells under these assay conditions is the reason that the LNCaP cells were not lysed. The results demonstrate that CTLs can be activated by immunogenic TARP polypeptides, and that these activated CTLs will lyse cancer cells that express HLA-A2.1, such as MCF-7 breast cancer cells.

6. To examine the frequency of peptide specific $CD8^+$ T cells in the prostate cancer patients, tetramers were made that were composed of individual peptides bound to HLA-A2.1. PBMC from prostate cancer patients were stained with anti-CD8 and tetramers. The TARP-29-

37 and TARP-27-35 tetramers detected $CD8^+$ T cells from the prostate cancer patients, but not the normal donors, suggesting that those tetramers could be used for detection of peptide-specific $CD8^+$ T cells.

7. These studies demonstrate that immunogenic fragments of TARP can be produced and used to activate lymphocytes, and that these immunogenic fragments can elicit cytotoxic T lymphocytes that can kill human cancer cells, and thus can be used for the treatment and detection of prostate and breast cancer. These immunogenic fragments and methods to test these fragments are fully disclosed in the specification of the above-referenced application. One of skill in the art, could readily use the disclosure of the above-referenced application to produce peptide fragments of TARP and test their immunogenicity, as evidenced by the data provided in this Declaration. Further, one of skill in the art could readily use the guidance provided by the specification to immunize prostate or breast cancer patients to induce a cytotoxic T lymphocyte response against TARP, which we have shown can kill human tumor cells. Indeed, a clinical protocol to implement this invention in cancer patients is being prepared.

8. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Ira Pastan, M.D.

11/9/04
Date

Jay A. Berzofsky, M.D., Ph.D.

Date

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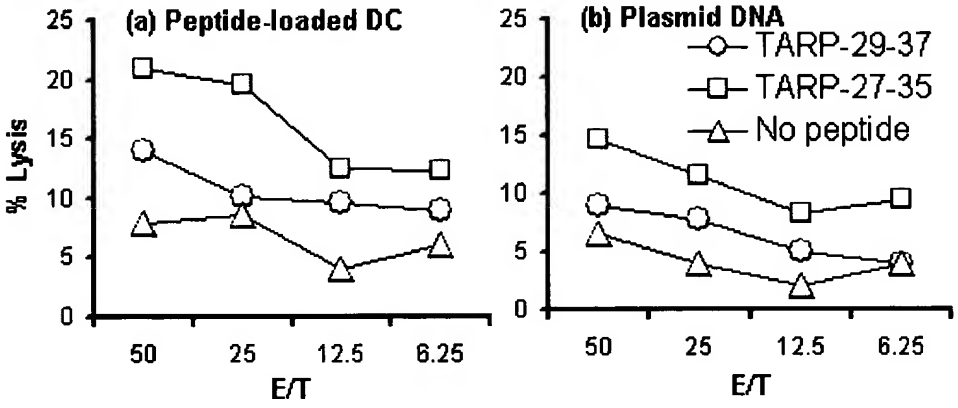

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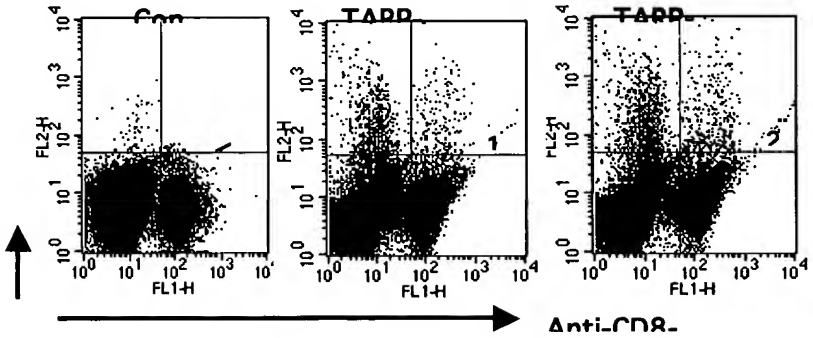

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Ira Pastan, M.D. — Date

Jay A. Berzofsky, M.D., Ph.D. — 8 November, 2004
Date

CURRICULUM VITAE

Name: Jay Arthur Berzofsky

Date and Place of Birth: April 13, 1946, Baltimore, Maryland

Marital Status: Married to Sharon M. Miller; two children
Alexander, April 30, 1974, and Marcus, May 27, 1976

Education:

1967 - A.B., Harvard University (Summa Cum Laude in Chemistry)
1971 - Ph.D., Albert Einstein College of Medicine, Molecular Biology
1973 - M.D., Albert Einstein College of Medicine, Medical Scientist Training Program

Brief Chronology of Employment:

1973 - 1974	Medical Internship (Straight Medicine), Massachusetts General Hospital, Boston, Massachusetts
1974 - 1976	Research Associateship, Laboratory of Chemical Biology National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health
1976 - 1979	Investigator ("Expert"), Metabolism Branch, National Cancer Institute, National Institutes of Health
1979 - 1987	Senior Investigator, Metabolism Branch, National Cancer Institute, National Institutes of Health
1987 - 2003	Chief, Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, National Institutes of Health
2003 – Date	Chief, Vaccine Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health

Honors/Awards:

Detur Prize, Harvard University, 1964
Harvard College Scholarship, Harvard University, 1964
Phi Beta Kappa, Junior Year, Harvard University, 1966
Summa Cum Laude in Chemistry, Harvard University, 1967
Sophia Freund Prize for Graduate with Highest Cumulative Grade Point Average, Harvard College, 1967
NIH Special Achievement Award, 1982
Hollister - Stier's Distinguished Lectureship, Washington State

University, 1986
J. W. McLaughlin Fund Distinguished Contributions to Immunology Lectureship, University of Texas Medical School, Galveston, 1987
U. S. Public Health Service Superior Service Award, 1988
31st Michael Heidelberger Award and Lecture, Columbia University, 1992
McLaughlin Visiting Professorship, University of Texas Medical School, Galveston, 1992
American Society for Clinical Investigation, President 1993-94
Fellow of the American Association for the Advancement of Science, 1995
Cytokine Interest Group Best Paper of 2000 Award to fellow in lab, 2001

Professional Society Memberships:

Association of Harvard Chemists, 1967 - present
New York Academy of Sciences, 1971 - present
American Association of Immunologists, 1977 - present
Undersea Medical Society, 1978 - 1988
American Federation for Clinical Research, 1979 - present
American Society of Biological Chemists, 1980 - present
American Society for Clinical Investigation, 1983 - present,
Secretary-Treasurer, 1989 - 1992
President-elect, 1992-1993
President, 1993-94
Association of American Physicians, 1990 - present

Editorial Positions:

Associate Editor, *Journal of Immunology*, 1980 - 1984
Editorial Advisory Board, *Journal of Molecular and Cellular Immunology*, 1983-88
Advisory Editor, *Molecular Immunology*, 1985 - 1988
Editorial Board, *Peptide Research*, 1987 - present
Transmitting Editor, *International Immunology*, 1988 - 2000
Editorial Board, *Journal of Human Virology*, 1997-present
Consulting Editor, *Journal of Clinical Investigation*, 1998-present
Section Editor, *Clinical Immunology*, 2002-present
Associate Editor, *Clinical Cancer Research*, 2002-present

Professional Committees and Activities:

American Association of Immunologists, Membership Committee, 1981 - 1988
American Association of Immunologists, Chairman of Membership Committee, 1983 - 1988
NIH Clinical Center Compensable Events Committee, 1982 - present
American Society for Clinical Investigation, Council, 1989-1994
NCI Division of Clinical Sciences Promotion and Tenure Committee, 1995-2001.
NCI Division of Clinical Sciences Research Advisory Group, 1995-2001
NCI Director's Intramural Advisory Board, 1997-99
NIH AIDS Vaccine Research Center Steering Committee, 1997-present

NIH Search Committee for Director of Office of AIDS Research, 1997-98
NIAID Malaria Vaccine Task Force, 1998-present
NCI Vaccine Working Group, Chairman/Organizer, 1998-present
NCI/CCR Immunology Faculty Steering Committee, 2001-present
NCI/CCR HIV & Virology Faculty Steering Committee, 2001-present
NCI/CCR Frontiers in Science Newsletter Editorial Board, 2001-present.
NCI/NIH Committee for Biodefense, founding member, 2001-present.
NCI Center of Excellence in Immunology, Steering Committee, 2003-present.
NIH CRADA 01361 with Genzyme Corporation. Co-principal Investigator, 2003-present

Military Service:

Commissioned Corps, United States Public Health Service, 1974 - 1976

Other Research Experience:

Summers,1962 - 1965 Research Assistant, Pediatric Research Unit (H. M. Nitowsky), Sinai Hospital, Baltimore, Maryland
Summer, 1966 Research Assistant, Organic Synthesis Laboratory C. H. Robinson), Department of Pharmacology, Johns Hopkins School of Medicine, Baltimore, Maryland
Summer, 1967 Visiting Scientist, Laboratoire d'Enzymologie (G. N. Cohen), Centre National de la Recherche Scientifique, Gif-sur-Yvette, France

Medical Licensure: Maryland and Massachusetts

Major Outside Activities

Medimmune, Inc.—Scientific Founder and Chair, Scientific Advisory Board, 1989-2002
Magainin Pharmaceuticals, Inc.—Member, Scientific Advisory Board, 1991-97
Diacrin, Inc.—Member, Scientific Advisory Board, 1993-2002
Pharmadyne, Inc.—Scientific Co-Founder and Chair, Scientific Advisory Board, 1997-present
Boston University Community Technology Fund—Consultant, 1997-present
Health Care Ventures, Inc.—consultant, 1998-present
EMD Pharmaceuticals, Inc.—consultant, 2000-present
Epivax, Inc.—Member, Scientific Advisory Board, 2000-present
Therapeutic Devices, Inc.—consultant, 2002-present
Transform Pharmaceuticals, Inc.—consultant 2002-present
Celera Genomics, Inc.—consultant 2002-present
Genencor International, Inc.—consultant 2003-present.

Major areas of research:

1. Molecular basis of antigen recognition by T lymphocytes
2. Processing of antigens and their presentation by major histocompatibility molecules
3. Structure of antigenic sites on protein antigens

4. Genetic regulation of the immune response
5. Design and development of artificial vaccines based on immunological principles and peptide synthesis or recombinant DNA technology
6. AIDS vaccines and diagnostic techniques
7. Malaria vaccines
8. Cancer vaccines
9. Antigen-antibody interactions
10. Structure-function relationships in proteins and protein conformation.
11. Regulation of tumor immunosurveillance and T cell function by cytokines
12. Mucosal immunity and vaccines